

Cupric Ion Release from Various IUD Geometries

BEE 4530 Computer-Aided Engineering: Applications to Biological Processes

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Executive Summary

Intrauterine Devices (IUDs) are gaining popularity as a form of long-acting reversible contraceptives (LARC); once inserted, copper IUDs can be effective for up to ten years and require no action from the user. The contraceptive effect of copper IUDs is believed to be at least partially due to the spermicidal effect of cupric ions in the uterine cavity, as well as the inflammatory immune response induced by the foreign object. The release of cupric ions depends on the surface area of copper, IUD geometry and physiological factors. Negative side effects from IUDs, such as pain and bleeding, are also related to IUD shape and uterine anatomy.

There has been increased interest in developing new IUD designs that minimize these unwanted side effects while maintaining contraceptive effectiveness. In order to implement new IUD designs, animal testing and clinical trials are stages in which prototypes are determined to be effective. To minimize risk, a computer-simulated model can predict how an IUD will behave in vivo. However, a computer-simulated model of cupric ion release from IUDs does not presently exist. Therefore, this study accomplished the goal of developing a physiologically accurate digital model of cupric IUD erosion patterns in the uterus.

By using COMSOL, a physiologically accurate model of an IUD in vivo was created. Then, the diffusion behavior of copper in two different domains – the uterine fluid and the blood – was simulated. Because the copper IUD will release copper ions as it erodes, the concentrations of copper in the two domains were dependent on the mass flux of copper out of the IUD. The concentration of copper in these domains was also affected by copper removal, which occurs through convective flux in the blood and cervical flux. The concentration of copper ions in the uterine fluid and blood were tracked over a period of 1 year.

As a result, this model allowed investigators to determine the parameters at which a digitally modeled copper IUD is most physiologically accurate. The T-shaped copper IUD can be accurately modeled in COMSOL by using accurate parameters and incorporating a periodic function for increases in copper flux throughout the menstrual cycle.

Introduction

Intrauterine devices are one of the most effective methods of birth control used today. Its reliability, effectiveness, relatively low cost and longevity make IUDs an extremely popular device in preventing pregnancy. There are two main types of IUDs on the market: hormonal IUDs and copper IUDs. Copper IUDs have been around since the early 20th century and have undergone a lot of changes in that time.

Multiple IUD geometries have been put to market over the years - most notably, the Lippe Loop with copper, the Gyne-Fix, and the T- and U-shaped IUDs which are manufactured by multiple drug companies. The motivation for different geometries is to increase IUD effectiveness while reducing pain and bleeding due to ill-fitting devices. Studies conducted by both Wildemeersch et al. and Hasson have found that the shape of an IUD and its positioning in the uterus can affect both its effectiveness and comfort-of-use [2,3].

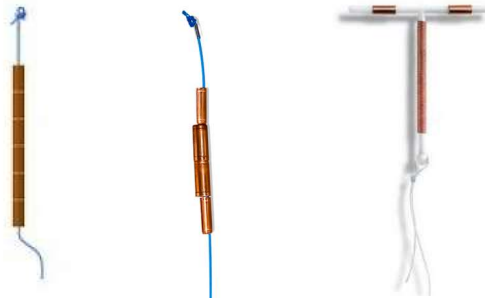


Figure 1. Common copper intrauterine devices used in the clinic today. The IUD designs above are frequently used by clinicians today for contraceptive use. From left to right, the IUD devices are the GyneFix, GyneFix mini, and TCU380A. Although the IUDs vary in initial copper surface areas, each IUD has proven to be an effective contraception through copper erosion.

The copper IUD functions as a contraceptive through a two-part mechanism: release of cupric ions into the uterine fluid and the foreign-body response of the uterus. Studies [1] have found that cupric ion release from IUDs is related to many factors, including the surface area of copper on the IUD and uterine physiology. A better understanding of cupric ion release from copper IUDs could aid in making smaller IUDs that are at least as effective in preventing pregnancy.

In this study, researchers will analyze the TCU380A IUD. The TCU380A, or T-shaped IUD, is comprised of copper wire wound around the stem of a T-shaped, polymer structure. Although this IUD design has proved to be effective, local corrosion can cause breakage in the copper wire. These wire fragments may lodge themselves in the endometrium, causing pain and increasing risk for infections [2]. The size and rigidity of the IUD can also cause pain and discomfort, possibly leading to early removal of the device or decreased quality of life for the user.

Problem Statement

An IUD's contraceptive effect depends on the release of copper into the uterine cavity as it erodes. The contraceptive effect is therefore correlated with the copper concentration in the cavity. For this reason, once an IUD has undergone significant erosion and has decreased its copper surface area, it loses effectiveness. Furthermore, the surface area required for contraceptive effect can necessitate a large IUD that increases negative side effects. The effective lifetime and size of an IUD are both determined through imprecise means. A physiologically accurate model of a copper IUD could improve the understanding of IUD function and lead to better designs.

Design Objectives

This model will accomplish the following objectives:

- (1) Simulate the change in mass transfer of copper ions in the uterine fluid and the blood over time as a result of cupric IUD erosion
- (2) Determine the values of unknown parameters
- (3) Generate an accurate physiological model for an IUD in the uterus

Problem Schematic

Because the model will assume identical behavior on each side of the axes of symmetry, only one quadrant of the model presented in Figure 2 will be analyzed. The copper IUD will release a constant flux of copper ions into the uterine tissue as it erodes, thus producing an increase in copper ion concentration in the uterine cavity, or the fluid between the IUD and the uterine walls. The model assumes the uterine fluid to be a static layer, which acts as a barrier rather than a flowing channel. The model will focus on the uterine fluid as the primary domain. Because the endometrium is extremely vascularized, the endometrium will quickly remove the excess copper ions during menses to prevent build up. The endometrium will have a convective boundary condition, as the copper will accumulate in this region before being swept away by the blood.

As fluid is passed through the cervix during menstruation, the copper will be removed from the uterine cavity. According to studies conducted by Oster & Salgo, when tested, the menstrual blood from patients with IUDs contains approximately half of the total copper concentration accumulated over the course of the month [7]. Figure 2 shows the 3D implementation of the IUD geometry in COMSOL.

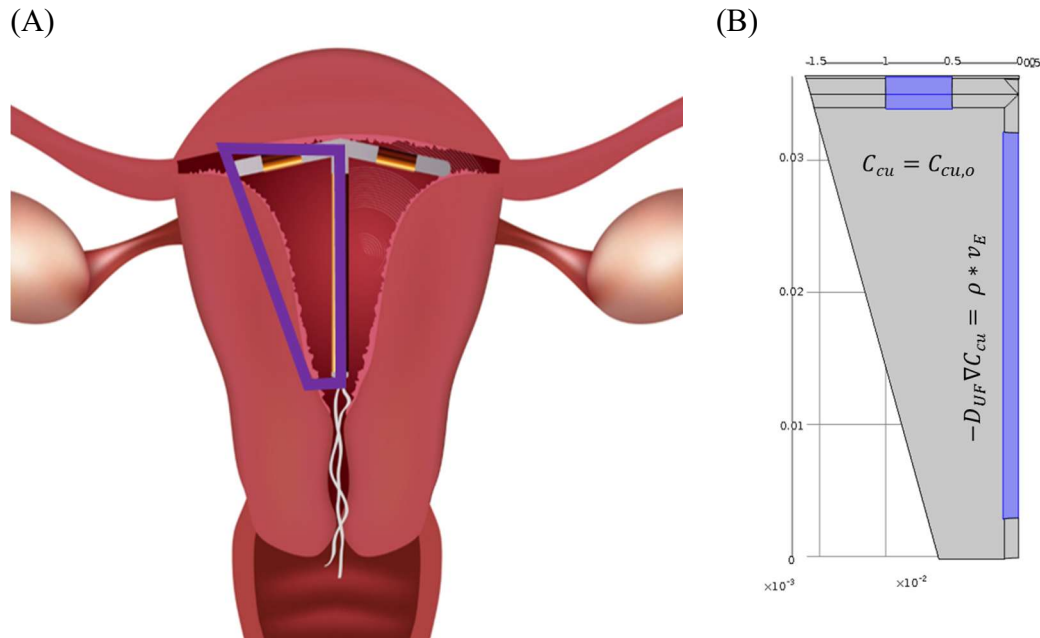


Figure 2. Three-Dimensional Adaption of Two-Dimensional Geometry. (A) This schematic of the uterus highlights the portion that will be examined in the 3D model (blue). See Figure 2A for the labeled components of the uterus. (B) This model offers a three-dimensional view of the uterine fluid with the imprint of the T380A IUD. The sections highlighted in purple correspond to the copper sections of the IUD. The boundary conditions and initial conditions are listed on the schematic at their respective regions. The copper portions of the IUD will emit a constant flux of copper ions, while the flux out of the cervix will provide a source of removal for the copper ions. The initial concentration of copper in the uterine fluid is CUF. Dimensions are given in meters.

Experimental Setup

The solution was implemented in COMSOL as an IUD immediately following insertion. Over a period of one year, an IUD will erode and emit a constant flux of copper ions [1]. This flux will provide contraceptive benefits to the patient, but be cleared from the uterus at a sufficient rate through the cervix, so as not to accumulate in the body at dangerous levels. Three different IUD geometries will be modeled using COMSOL over the given time period, and the optimal IUD geometry will be determined through the use of an optimization function in the subsequent phases of this project.

Implementation in COMSOL

The geometry presented in Figure 3 was used to model the erosion of the IUD as a 3D problem with three physics: transport of dilute species, global ODEs and deformed geometry. Two different boundary conditions were applied to the geometry to maintain the movement of copper at these locations, including the interface between the uterine fluid and the cervix. When these components were computed, they produced a concentration profile of the uterus after one year. Additionally, the mass flux of copper ions from the IUD was calculated through the use of an integration coupling along the surface area of the IUD, and the accumulation of copper ions in the body was calculated using an integration coupling along the uterine cavity boundary.

Transport of Dilute Species

The following governing equation was used to describe the mass transport of cupric ions in the uterine fluid over a specific time period in three-dimensional space.

$$\frac{\partial C_{cu}}{\partial t} = D_{UF} \nabla^2 C_{cu} - R_{UF} \quad (1)$$

Where C_{cu} is the concentration of copper in the uterine fluid, D_{UF} is the diffusivity of the uterine fluid, and R_{UF} is the periodic removal of copper from the uterine fluid. Copper, as well as the uterine lining, is removed from the uterus for an average time of 4 days. On average, this will occur once every 28 days. During menstruation for a patient with an IUD, approximately half of the total copper lost from the IUD is passed through the cervix [7]. Investigators have defined this copper flux with the step function, R_{UF} , where the function is “on” for 4 days, and “off” for the remaining 24 days. The function R_{UF} acts as a degradation term in the uterine fluid to represent the copper loss due to menstruation.

Investigators also considered the removal of the endometrial wall as a significant factor in copper erosion and the amount of copper entering the uterus during menstruation to be later expelled through the cervix. This was accounted for as a periodic, rectangular flux function.

$$N_{end} = \frac{C_{blood} \cdot V_{end,avg}}{SA_{uterus}} \quad (2)$$

Where N_{end} is the flux of copper as a result of endometrial shedding, $V_{end,avg}$ is the average volume of the endometrium [14], and SA_{uterus} is the surface area of the uterus.

Investigators then addressed the concentration of copper in the blood. As the copper diffuses into the uterine fluid, the copper concentration in the blood will change. The concentration of copper in the blood, C_{blood} , is affected by both the removal variable R_{blood} which accounts for the degradation of copper in the body, and the copper flow out of the uterine walls into the bloodstream $C_{in\ blood}$. This value, $C_{in\ blood}$, depends on the uterine copper concentration, and $C_{in\ dietary}$, a constant amount of ingested copper. As a result, the concentration of copper in the blood will be characterized by the coupling of these variables in the following equations.

$$\frac{\partial C_{blood}}{\partial t} = C_{in\ blood} + C_{in\ dietary} - R_{blood}C_{blood} \quad (3)$$

$$C_{in\ blood} = \frac{4 \int h_{ss}(Cu - Cu_o)dA}{Vol} \quad (4)$$

$$C_{in\ dietary} = R_{blood} \cdot C_{blood\ init} \quad (5)$$

These equations represent a simplified model of the copper behavior in the uterine geometry.

Boundary Conditions

The removal of excess copper from the uterus into the endometrium, or uterine wall, is treated as a convective boundary condition at the uterine wall. The blood, a highly vascularized region of tissue, will be treated as a layer along the uterine fluid that essentially sweeps the copper away with convective boundary condition.

$$D_F \nabla C_{cu} = h_{ss}(C_{cu} - Cu_o) \quad (6)$$

where h_{ss} is the mass transfer coefficient of the endometrium and D_F is the diffusivity of copper in the blood.

The transfer of copper from the IUD is treated as a set flux along the copper regions of the IUD.

$$D_F \nabla C_{cu} = \rho \cdot v_E \quad (7)$$

Where ρ is the density of copper, and v_E is the erosion velocity of the copper IUD.

Initial Condition

The initial condition for the transient solution assumes the initial concentration of copper at the in the uterine fluid be a particular value, C_{UF} , at the start of the time-dependent solution. Every other location on the schematic will be assumed to be the value of $C_{blood\ init}$.

Methods & Results

Mesh Convergence

A mesh convergence analysis was performed on the 3D geometry to determine the optimal mesh size for this model. In order to minimize discretization error, the solution must be computed with the proper mesh size. Optimal mesh size was determined by plotting the concentration of copper at a specific point in the uterus, and then gradually increasing the number of elements. Investigators then observed the effect of the mesh size on the solution, specifically the effect on the independent variable. When the solution for the independent variable reaches a steady-state, i.e., no longer changes, then the optimal mesh size has been discovered. The mesh convergence analysis is shown in Figure A1 in Appendix A, and the final mesh is pictured in Figure 4.

The optimal mesh setting was determined by plotting the copper concentration of the cut point shown in Figure 4 after 28 days with seven different mesh settings. The mesh settings were selected from the unstructured physics-controlled mesh settings defined by COMSOL, including coarser, coarse, normal, fine, finer, extra fine, and extremely fine, as indicated on the plot. Because the solution converges at the fine mesh point, investigators have chosen to use the fine mesh domain element size, which is 10,082 domain elements.

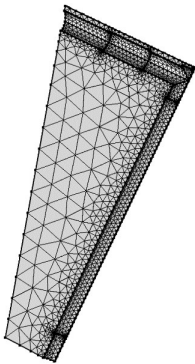


Figure 3. Optimal IUD and Uterine Fluid Domain Mesh. After completing a mesh convergence analysis, the optimal unstructured mesh was determined to be the Fine, Physics-Controlled mesh setting, provided by COMSOL. The number of domain elements was 10082, the number of boundary elements was 5258 boundary elements, and the number of edge elements 654.

After obtaining the proper setting for the domain mesh, the results for the copper concentration in the uterus and blood were computed. The following plots were obtained: surface plots of the concentration of copper in the uterus after 1 year, average copper concentration in the blood and the uterine fluid, volume deformation plots, concentration plots of specific points within the uterine fluid for comparison, and plots for the behavior of the erosion velocity over 1 year.

Surface Plot

After the insertion of the IUD, the expected duration of contraception is approximately 5-10 years [3]. Because the IUD devices reach equilibrium at approximately 6 months, the surface plot of concentration has been presented in this model after 1 year [5].

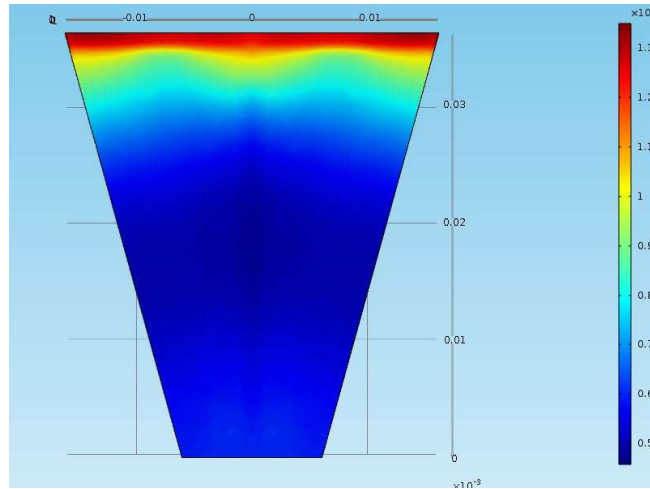


Figure 4. Surface Plot of Copper Concentration after 1 year. Dimensions of the fourth of the uterus in the schematic are 2 cm at its widest at the fundus, and 0.5 cm at its narrowest at the cervix. Dimensions of the IUD are 1.1 mm in diameter and 5 cm in height. The plot was generated by using the mirror function in COMSOL, after a period of 364 days. The concentration, given in in ug/dL, is clearly lower by the cervix due to the copper lost during menstruation.

In order to gain an understanding of the relationship between the concentrations of copper in the uterus, as compared to the concentration of copper in the body, investigators produced a plot of the average uterus concentration as a function of time over the course of 365 days. This plot will also allow investigators to observe the changes in copper concentrations over the entire time period, rather than just the final result.

Average Concentration Plot

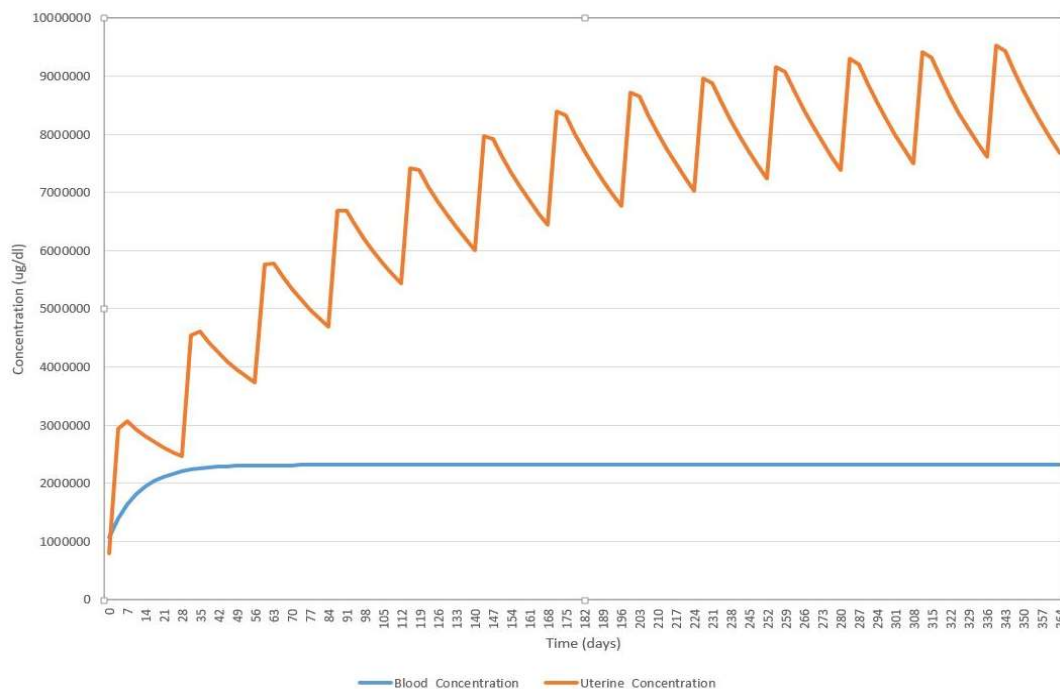


Figure 5. Average uterine copper concentration and blood concentration plotted over 365 days. The blood concentration of copper approximately doubles during this time period. The uterine concentration shows cyclical variations caused by menstruation. Towards the end of the year, the concentrations can be seen to be reaching steady state.

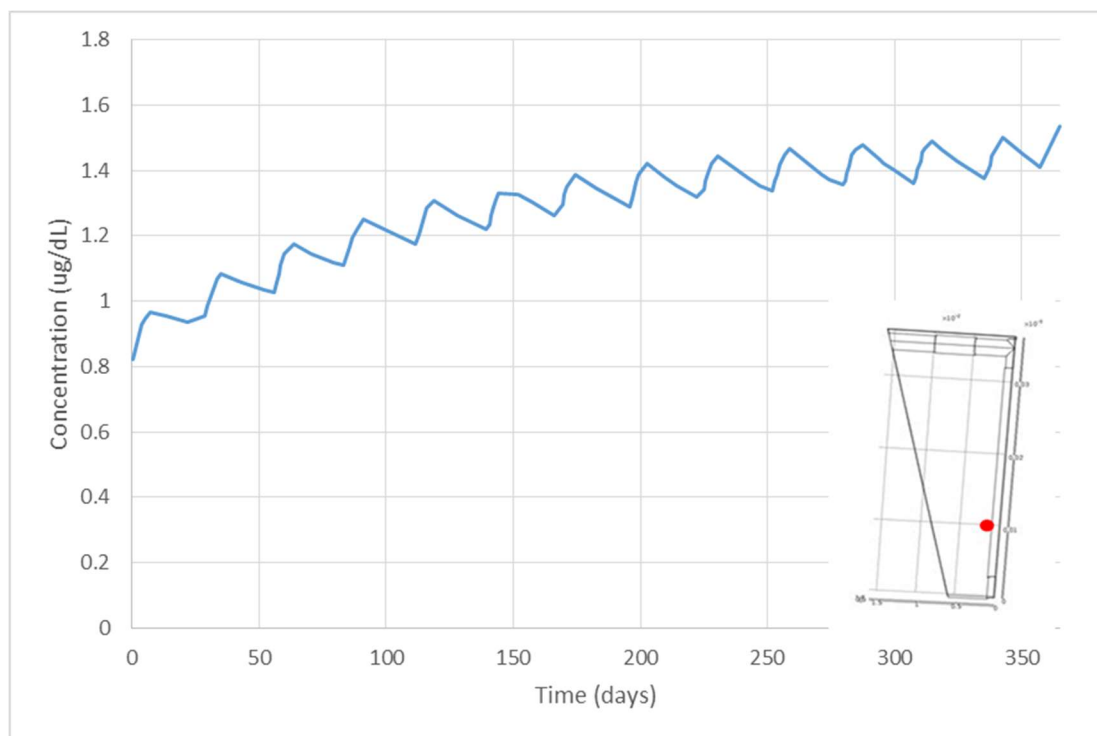
Figure 6 shows the convergences of both the uterine fluid and blood concentrations of copper to constant values. The concentration of copper in the body is higher than the uterine concentration at first, but concentration of copper in the uterus eventually surpasses the body concentration. These results will later be confirmed by a comparison to literature values.

After having gained a global understanding of the changes in copper concentration in the uterus over the target time period, investigators showed the changes in copper concentration at specific locations in the uterine fluid

Cut Point Plots

Cut point plots at the locations shown in Figures 7A and 7B, respectively, have been included to display the change in concentration over time at selected points in the uterine fluid. The point represented in Figure 7A shows a segmented increase in concentration over time and is positioned closer to the IUD in the uterus, while the point represented in Figure 7B shows a two-part increase: first a steep linear increase, then a more gradual linear increase and is positioned farther from the IUD in the uterine cavity.

(A)



(B)

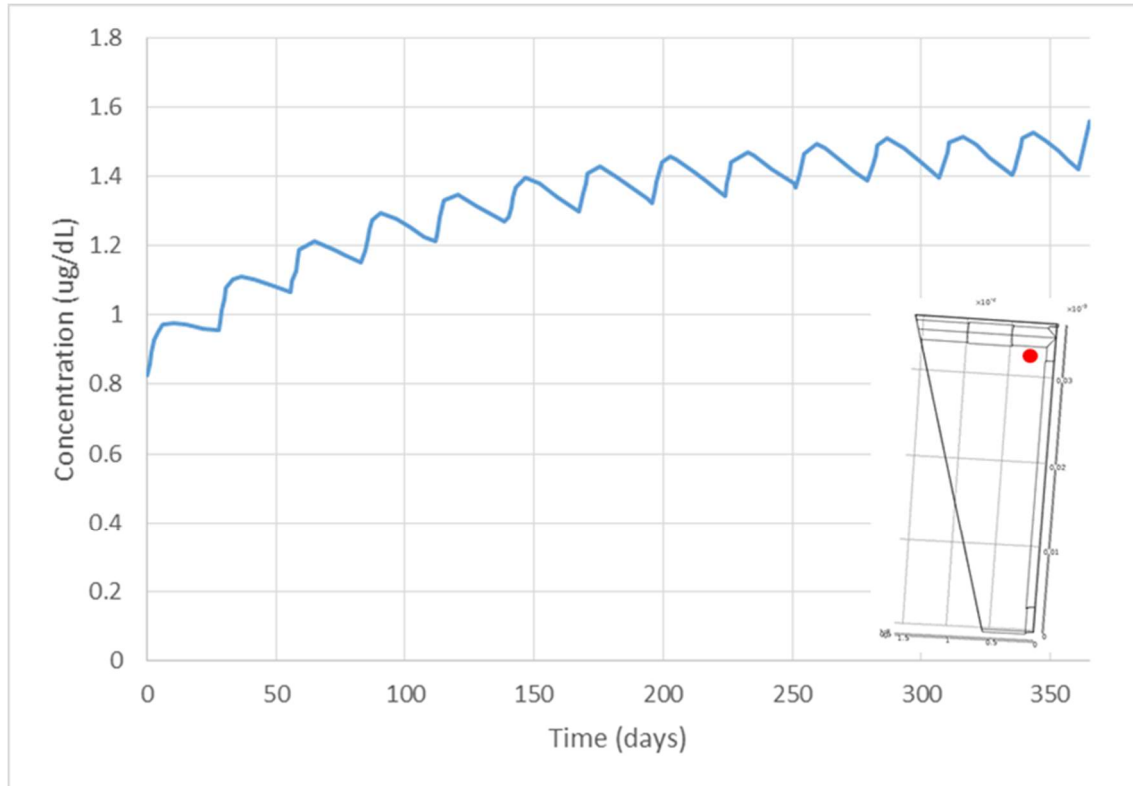


Figure 6. Cut Point Plots in Various Locations in the Uterine Fluid. (A) The concentration of copper at $(x,y,z)=(0.00091, 0.0025, 0.0325)$ m vs. time during the study. (B) The concentration of copper at $(x,y,z)=(0.0001, 0.0013, 0.01)$ m vs. time during the study. For each of the point plots, the point in the geometry is indicated on the left by the red dot.

When comparing the selected points, the graphs show that the concentration of copper in the uterus increases more drastically at the point closer to the IUD. Additionally, although the average concentration of copper in the uterus will fluctuate in a cyclical manner, individual points within the uterus do not. Instead, these points will increase to a steady-state value and remain constant.

In order to better understand the copper fluctuations in the uterine fluid and the blood, investigators then examined the changes in structure of the IUD. The IUD will erode over time, thus releasing copper into the uterine fluid to serve as a contraceptive. The following plot shows the change in the volume of the IUD over time, as the IUD erodes.

Volume Deformation Plot

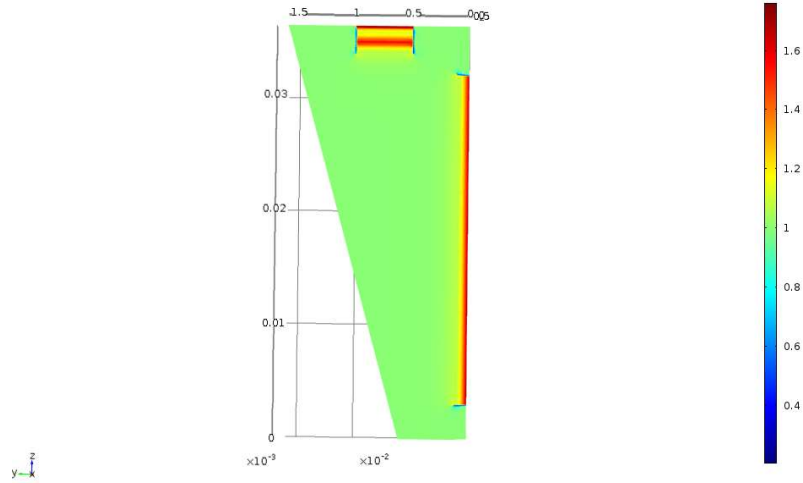


Figure 7. Ratio of volume gained by erosion across the domain after 365 days. Due to copper loss to erosion, the uterine fluid gains volume during the study. The ratio of the volume gained to the initial volume indicated that the most erosion occurs at the edges of the copper, because the copper domain gets smaller, as would be expected. The legend to the right shows the ratio of volume gained to the original volume.

Figure 8 confirms the erosion of the IUD because the regions of the uterine fluid that are in contact with the copper domain have gained volume. For these regions of uterine fluid, the ratio of volume gained ranges from 1.1 to 1.7. The fluid around the copper domains will fill the space left by the copper, thereby increasing in volume. Researchers further investigated the structural changes of the IUD by determining the rate at which the IUD degrades.

Erosion Velocity

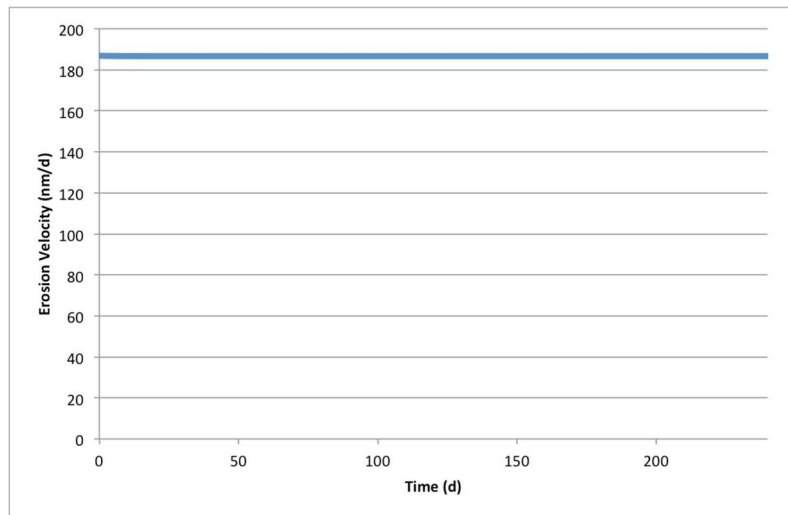


Figure 8. Plot of erosion velocity over time. Within the uterus domain, the erosion velocity of the IUD reaches a value of 186.7 nm/d and remains constant over a period of 150 days.

The erosion velocity remains constant over the course of 240 days. This plot indicates the presence of erosion, and therefore, the decreasing mass of copper in the IUD due to erosion. The erosion rate was also used as a method for model validation.

Model Validation

In order provide validation for the COMSOL model, computed values were compared to values reported in the literature. Researchers aimed to produce values that were on the same order of magnitude as the literature values. The following variables were used as benchmarks for accuracy checks: erosion velocity and the steady-state copper concentration in the blood with an IUD. Table 1 shows the comparison of the value computed through COMSOL with the given literature value.

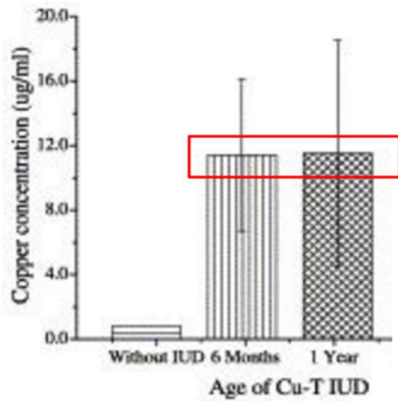
Table 1. Literature values compared to computed values for accuracy check. The following values were gathered from the literature, and used as a target for the COMSOL models. These values are also listed separately in Table 2 of the appendix. The COMSOL model is valid, being that the parameter values are all within the same orders of magnitude, respectively.

Parameter	COMSOL Value	Literature Value
Erosion Velocity	186.7 nm/d	108.7 nm/d
C _{body} at steady-state	230 ug/dL	217.51 ug/dL

The reported literature value for erosion velocity was 43.8 ug/day, which is 108.7 nm/d when converted to the reported COMSOL units. The calculated COMSOL value for erosion velocity was 186.7 nm/d [12]. Because these values are within the same order of magnitude, this ensures that investigators have created an accurate COMSOL solution. Additionally, when comparing the steady-state literature values of copper concentration in the body with the computed values, the computed values are in the proper range, as they are of the same order of magnitude. The concentration of the copper in the body at steady-state in the body is reported at 217.51 ug/dL [5]. For the uterine fluid copper concentration, the literature indicated that it should increase several fold during the first 6 months after insertion and then plateau for the next 6 months [5]. Currently, the COMSOL model shows the same plateau, but the magnitude of the increase is much smaller.

The model was further validated by the trends posed in the literature for copper concentration cycles. In her study, Veronica Arancibia determined the copper concentrations from uterine fluid samples in 27 women [5]. The graphs generated in the study represent the physical copper values and can be matched to the trends produced by the COMSOL model. Figures 10 and 11 highlight the similarities between the physical values and digital values.

(A)



(B)

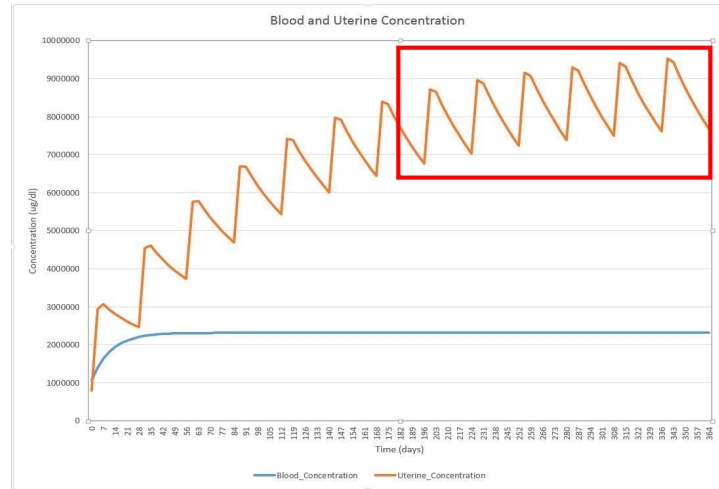
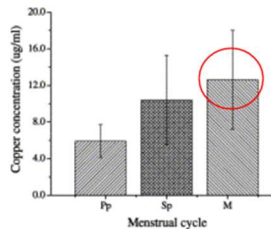


Figure 9. Concentration of copper in the uterine fluid will reach a steady-state value after 1 year. The concentration of copper in the uterus, as shown in the COMSOL (B), reaches a steady-state value after approximately 6 months. This trend is reflected in the concentration of copper in the uterus in the female patients, being that the concentration of copper in the uterus reaches a constant value after 6 months, as shown in the graph in (A) [5].

(A)



(B)

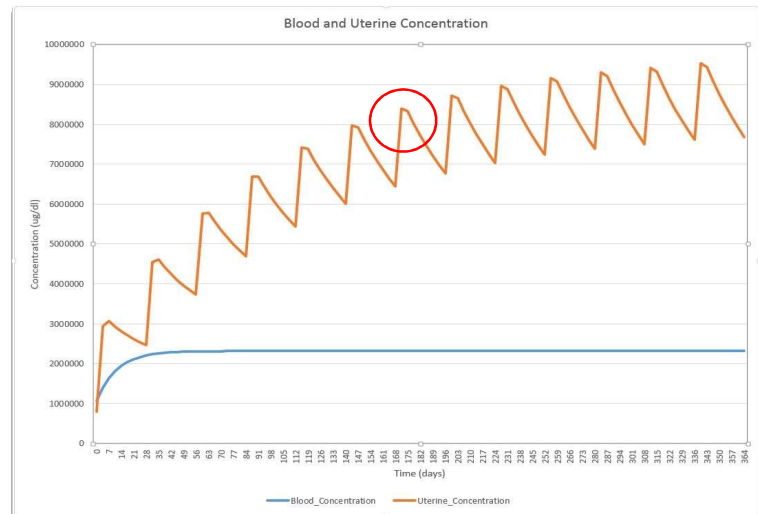


Figure 10. Concentrations of copper will fluctuate in response to menses. The concentration of copper in the uterus shows a cyclical behavior, as a result of the shedding of the endometrial tissue. The concentration of copper will then decrease over the course of the cycle in the secretory and proliferative phases. This trend is shown in both the COMSOL plot (B) and the physical values of copper in the uterine fluid (A) [5].

Sensitivity Analysis and Parameter Tuning

For sensitivity analysis, the investigators decided to test the effects of varying the diffusivity of copper, the magnitude of the menstrual flux, the copper degradation in the body and the value of our blood mass transfer coefficient. A parametric sweep was run to determine values not found in the literature. By running the sensitivity analysis, investigators hoped to confirm our current values or identify more appropriate values.

A parametric sweep was run for the diffusivity analysis for 4 different orders of magnitude for two months. The hope was that the solution wouldn't change that much with the diffusivity. If it did change, this change should cause more accumulation in the blood and uterus to better reflect the literature values. In the end, significant changes resulted as the diffusivity was varied. On both the high end and the low end of the diffusivity values, the "period effect" disappeared from our graphs. This is due to there being no copper throughout the uterine fluid or copper that diffuses so fast that there is no visible change due to the period. Therefore, we decided to go with the value that allowed there to still be the visible period effect.

For the blood degradation constant, a parametric sweep was run for 2 months at a total of 9 different orders of magnitude. The ideal degradation constant would have resulted in a doubling of blood concentration. When the value was too high, the blood copper concentration decreased to zero, which was clearly unrealistic. When it was too low, it increased linearly to infinity, which was also clearly unrealistic. A value was eventually found that matched the expectations and the qualitative behavior in the literature.

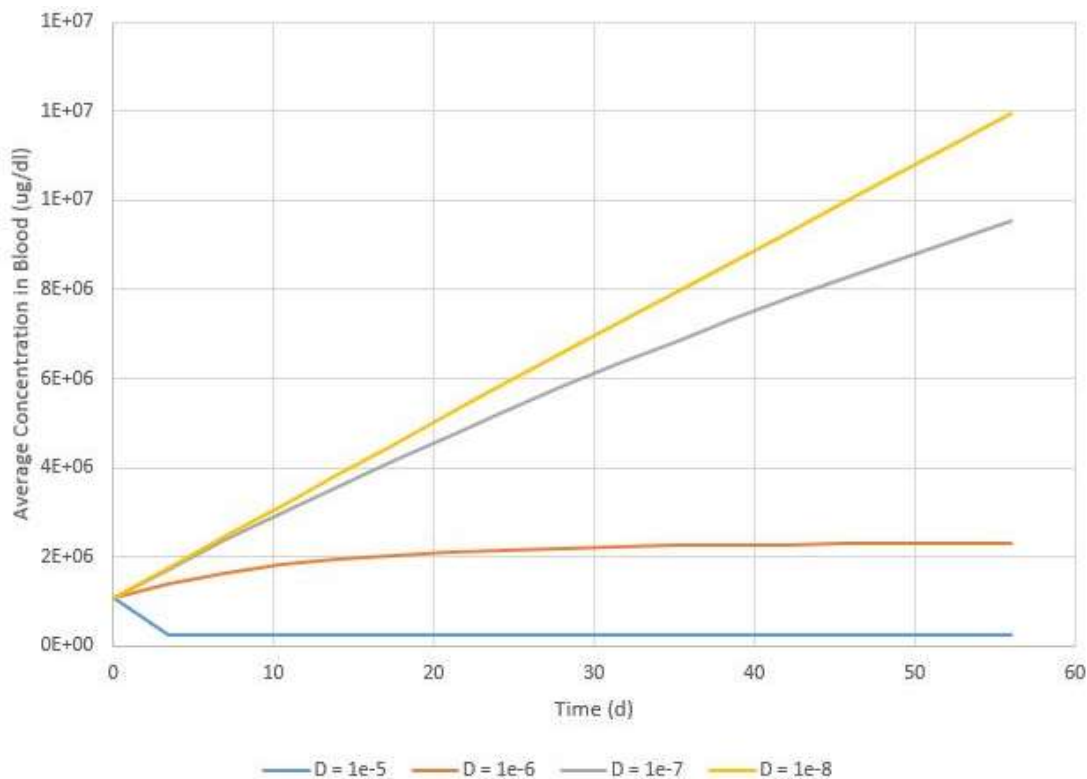


Figure 11. Plot showing four different values of the blood degradation constant and the effects on the blood copper concentration. The value of 1×10^{-6} [1/s] was chosen.

For the blood mass transfer coefficient analysis, another parametric sweep was done for the possible values. The ideal value would allow for an accumulation of copper in the uterus that plateaued at around 6 months. The value should not cause the uterine concentration to stay constant or increase monotonically.

For the menstrual flux analysis, a parametric sweep was run with fluxes that spanned four orders of magnitude for 2 months.

During the sensitivity analysis, it was found that all four chosen parameters had significant effects on the model. Therefore, the qualitative behavior found in the literature was used to choose values.

Conclusion

Our COMSOL model represents the first step in creating an accurate computational model of copper IUD degradation within the uterus. Though simplified, our model was able to match literature values for blood and uterine copper concentration while accounting for the effects of both menses and copper erosion.

Because our model can be easily modified to reflect other IUD geometries, it has the potential to aid in future research into new IUD designs without the need for human studies. It can also be modified to reflect varying uterine geometries, menstrual patterns and time scales. This could help improve the understanding of how IUDs work and how they can be further improved. Given how many IUD side effects are related to it being too large or there being too much copper, the ability to predict the behavior of the IUD could greatly improve designs.

This first step that we have taken should be followed by increasing the accuracy of the model and expanding its applicability. Our simplified and idealized model of the uterine geometry can be replaced with a more realistic model derived from CT scans. With a more accurate model of copper utilization and uptake in body, future designs can give a better prediction of the increase in blood copper concentration. This would allow researchers to take this into account when designing a new IUD.

Appendix A

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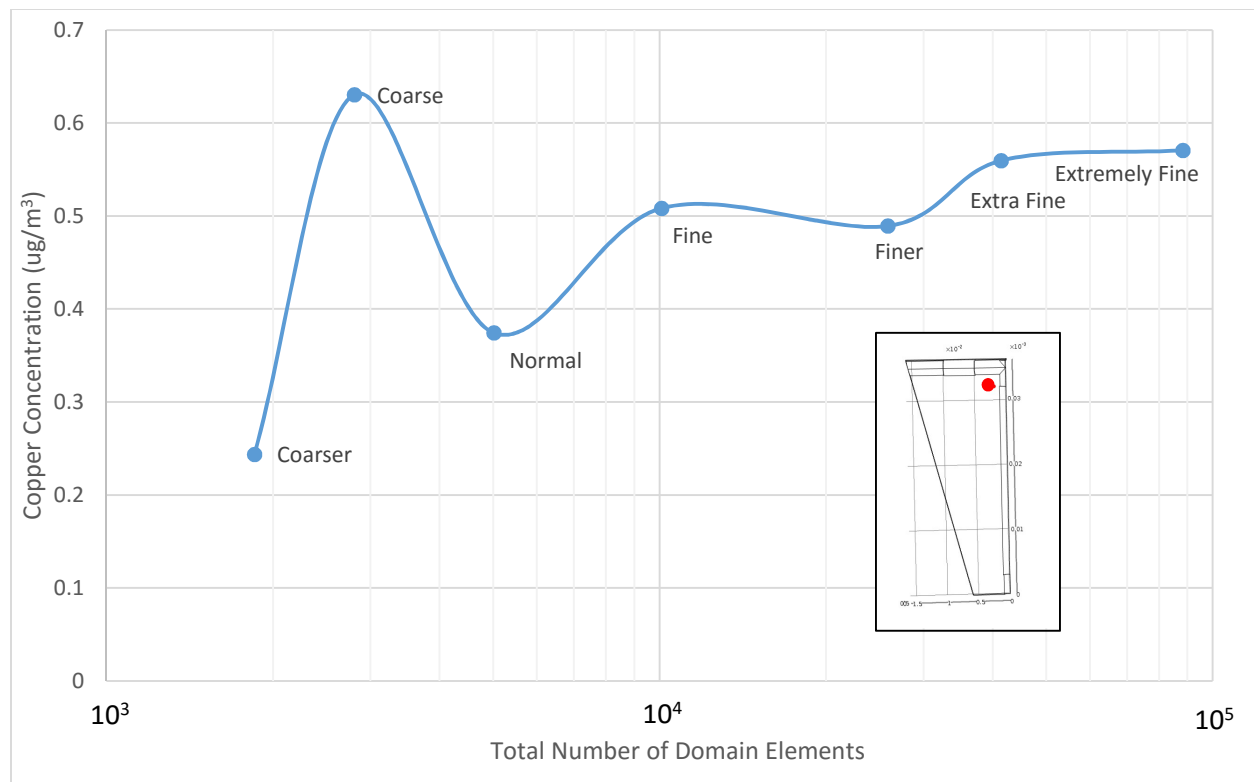


Figure A1. Mesh Convergence Analysis. Investigators examined the copper concentration at a point within the uterus domain, as shown on the graph by the red dot. The plot indicates that the mesh convergence occurs at both the fine mesh point, and then again at the extra fine mesh point. Investigators have elected to use the fine mesh because using an extra fine mesh will require vast amounts of computing power, without making the solution more accurate. Additionally, more parameter values will be added to the solution that should increase the viability of the mesh convergence analysis.

Table A1. Relevant Parameters for COMSOL computation. The following parameters were obtained from literature values, calculated manually, or estimated with parametric analysis.

Parameter	Symbol	Value	Units	Source
Uterine fluid copper diffusivity	D_{UF}	$1 \cdot 10^{-12}$	m^2/s	Calculated
Density of blood	ρ	1060	kg/m^3	10
Molecular weight of solute	amu	63.46	g/mol	8
Mass transfer coefficient of the blood for copper	h_{ss}	$1e-10$	m/s	Calculated
Blood volume	V_b	5	L	9
Degradation rate of copper	R_{blood}	$1 \cdot 10^{-6}$	$1/s$	Calculated
Erosion velocity of copper	v_E	43.8	ug/day	12
Initial uterine fluid copper concentration	C_{UF}	0.8	ug/ml	5
Initial blood copper concentration	C_{blood}	107	ug/dl	2
Average dietary copper requirement	$C_{in\ dietary}$	0.7	mg/day	13
Uterine degradation rate	R_{UF}	32	$mol/m^3 \cdot s$	Calculated
Periodic endometrial flux	N_{end}	Comsol eqn	$ug/m^2 \cdot s$	14